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Extended Summaries SCI Pesticides Group and RSC Biological and Medicinal Chemistry Group Symposium: Advances in the Chemistry of Crop Protection

The following are extended summaries based on papers presented at the meeting 'Advances in the Chemistry of Crop Protection' organised by P. J. Crowley, G. Mitchell, G. Keen, J. Pickett and P. D. Riordan on behalf of the SCI Pesticides Group and the RSC Biological and Medicinal Chemistry Group and held on 9–11 September 1996 at Churchill College, Cambridge. The contents are entirely the responsibility of the authors and do not necessarily reflect the views of the Editorial Board of Pesticide Science.

Synthesis of Analogues of Cispentacin, 1*R*, 2*S*-2-Aminocyclopentanecarboxylic Acid

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Cispentacin is the 1*R*, 2*S* enantiomer of 2-aminocyclopentanecarboxylic acid (Fig. 1, **1** X = CH_2). It was isolated independently by two groups from *Bacillus cereus*[1] and *Streptomyces setonii*[2] and shown to exhibit potent antifungal activity *in vivo* against *Candida albicans*.

The racemic compound was also claimed to exhibit activity against pathogens of agrochemical interest,[3] and a sample was prepared and tested at Jealott's Hill. Interesting levels of antifungal activity were observed against Phycomycete pathogens both in the glasshouse and in the field and hence a series of analogues were prepared.

It was envisaged that 4-substituted analogues of type **1** would be accessible using the chemistry outlined in Scheme 1 (Fig. 1), in which the amino functionality is introduced by Curtius reaction of the half-acid derived from an appropriate meso-diester. Scheme 2 illustrates this approach for the carbocyclic series. The diester **3** was prepared by oxidation followed by Ruzsicka-type cyclisation of the diester **2**, a modification of chemistry originally developed by Gais *et al.*[4] Hydrogenation of **3** selectively removed the benzyl group to give the desired half-ester **4**. Curtius reaction with diphenylphosphoryl azide gave solely the allophanate **5**, but use of trimethylsilyl azide on the corresponding acid chloride under carefully controlled conditions gave the desired carbamates in yields up to 70%. Analogues **7**–**11** are representative of the targets synthesised using this chemistry. The stereochemistry of the Curtius reaction was proved by removal of the keto-group in **6** by Clemmensen reduction and comparison with the appropriate protected cispentacin.

The Curtius chemistry was extended to the synthesis of other substituted analogues (Fig. 2, Scheme 3). The cyclopentane ring was first built up by annulation of 1,2-bis(4,4-dimethyl-2-oxazolin-2-yl)ethane with propanes bearing 1,3-leaving groups in the manner described by Yamamoto.[5] The *trans*-cyclopentane-1,2-diacids thus available could be converted to the corresponding *cis*-anhydrides by heating with propionic anhydride. The desired analogues were then available by application of the chemistry previously described. The 4-spirocyclopropyl analogue was, for example, one compound approached using this method.

The 1,3-dipolar cycloaddition chemistry envisaged for the synthesis of 4-heterosubstituted analogues (Scheme 1) was successful only in the case of nitrogen substitution. Scheme 4 (Fig. 2) shows how this chemistry was reduced to practice. The desired sulfur analogues were finally prepared by oximation/reduction of the Dieckmann adduct, 2-methoxycarbonyl-3-oxotetrahydrothiophene. The equivalent oxygen-substituted

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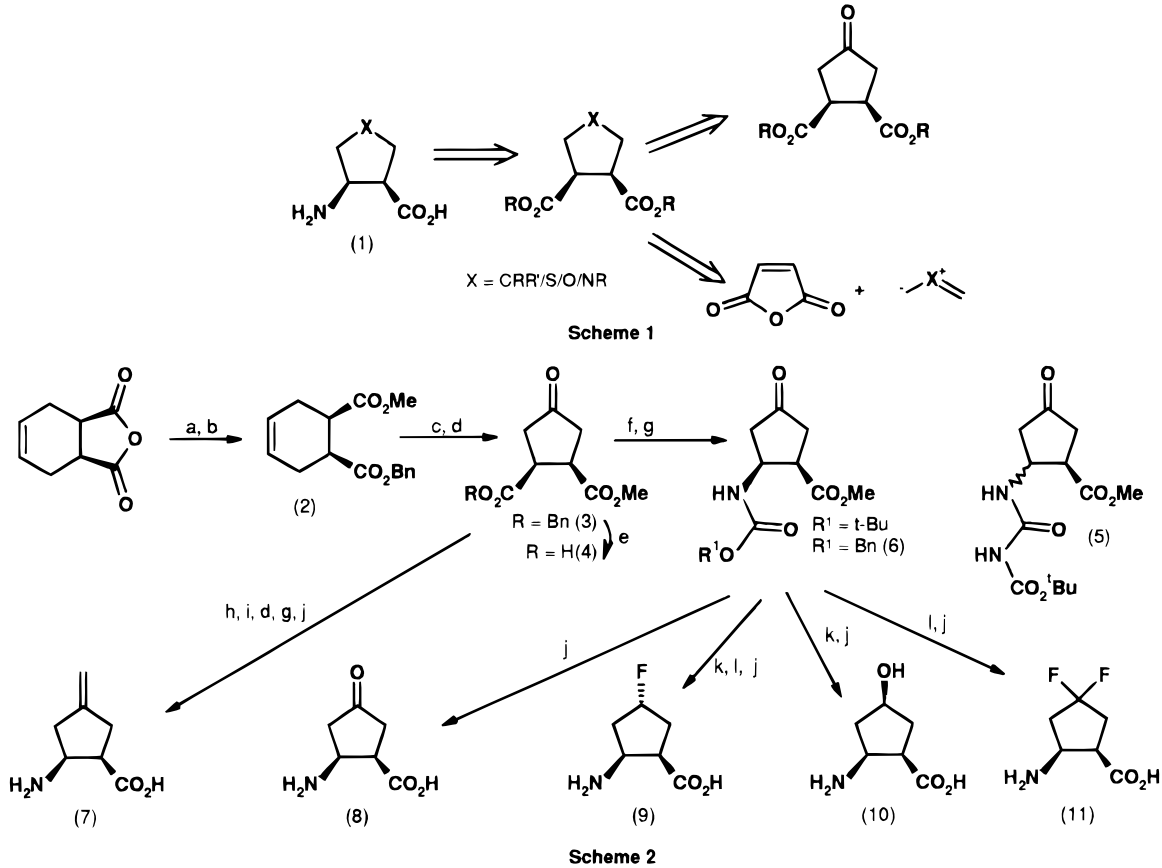

Fig. 1. Schemes 1–2. (a) NaOMe; (b) BnBr/DBU; (c) $KMnO_4$; (d) Ac_2O; (e) H_2/Pd; (f) Oxalyl chloride; (g) $TMSiN_3/R^1OH$; (h) CH_2I_2/Zn; (i) LiOH; (j) HCl; (k) $NaBH_4$; (l) DAST.

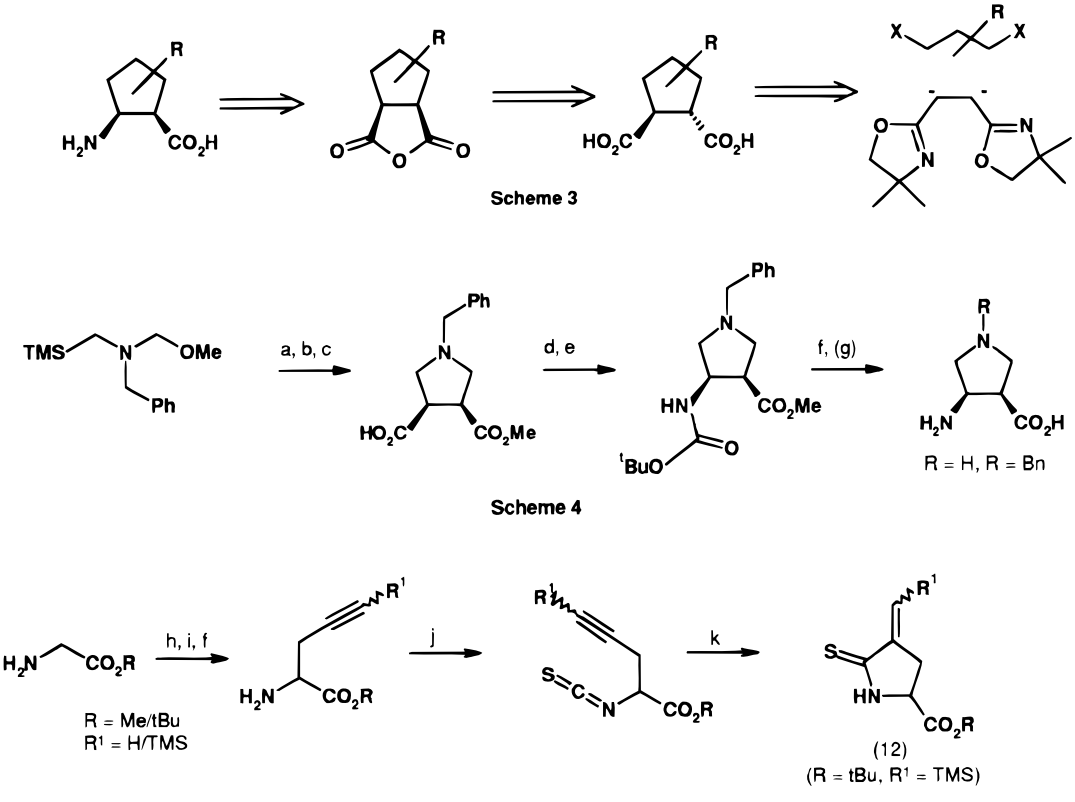

Fig. 2. Schemes 3–5. (a) Maleic anhydride/H_3O^+; (b) Ac_2O; (c) NaOMe; (d) Oxalyl chloride; (e) $TMSiN_3/R^1OH$; (f) HCl; (g) H_2/Pd; (h) Benzophenone imine; (i) LiHMDS/Propargyl bromide; (j) Thiocarbonyl diimidazole; (k) [i] $(TMS)_3SiH$/AlBN [ii] SiO_2.

compounds were prepared by stereospecific *cis*-hydrogenation of 2,3-di(methoxycarbonyl)furan followed by the Curtius sequence previously described.

5-Alkyl substituted analogues proved particularly interesting from a biological standpoint. 2-Amino-5-methylcyclopentane-1-carboxylic acid was synthesised by 2 + 2 cycloaddition of chlorosulfonylisocyanate with 3-methylcyclopent-1-ene (followed by separation of the complex mixture formed). The lack of generality of this method prompted us to investigate an approach in which the necessary substituted cyclopentane-1,2-diester precursor was made by tandem radical addition/cyclisation of substituted propargyl iodides with dimethyl maleate.[6] Ultimately, this approach proved unsatisfactory because the Curtius sequence on the resulting diesters was not successful. However, the success obtained with the initial radical cyclisation prompted us to apply radical chemistry in a related project, the synthesis of analogues of the fungicidal natural product 4-methyleneproline. Scheme 5 (Fig. 2) shows the realisation of a radical approach to the analogues **12**.[7]

Several of the cispentacin analogues described in this paper showed good levels of activity against Phycomycete pathogens.[8] In glasshouse tests, the 4-exo-methylene derivative **7** was slightly more active than racemic cispentacin. A series of patent publications describe the good activity of this compound against human pathogens and also disclose other compounds whose synthesis we have described.[9]

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α-Hydroxyarylacetamides: A New Class of Fungicidally Active Compounds

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The synthesis and subsequent discovery of fungicidally active α-hydroxyarylacetamides originated from a report that phenyltartronic acid amides exhibited insecticidal activity.[1] The slow-acting nature of this activity led us to speculate that these compounds might be metabolically activated via hydrolysis and then decarboxylation of one of the amide moieties. Subsequently, a synthesis programme looking at a wide range of α-hydroxy-arylacetamides was instigated. This yielded, not a new insecticide, but a novel class of fungicidally active compounds of which compound **1** (Fig. 1) was an early example.[2,3] A systematic study of the optimal substitution patterns in the two phenyl rings indicated that, while various electron-withdrawing groups in the 4- or 3,4-position of the mandelic acid ring gave good activity, very little change was allowed in the phenethylamine ring. One of the best analogues was compound **3** which showed very good activity (>95% control at 50 mg litre^{-1}) against both vine downy mildew (*Plasmopara viticola* Berl. & De Toni) and potato late blight (*Phytophthora infestans* (Mont.) de Bary.

During the next stage of our optimisation studies we systematically sought to modify the bridge connecting the two phenyl rings. This work resulted in the discovery of the biologically interesting methyl-substituted analogues **4** and **5**. The phenylisopropylamide **5** showed the best overall activity seen to date, and we were keen to investigate whether or not there was any biological discrimination between the four stereoisomers. The isomers were separated using chiral HPLC and the highest activity with respect to late blight was found to be associated with the two isomers possessing the *R*-configuration at the phenylisopropylamide centre (Table 1). This suggests that, for this pathogen, this chiral centre is biologically more important than that associated with the mandelamide end of the molecule. The absolute configuration of the phenylisopropylamine was assigned via an asymmetric synthesis.[4]

The two aryl groups of the α-hydroxyarylacetamide structure are joined by six bonds, of which only one, the amide bond, has any conformational restriction on

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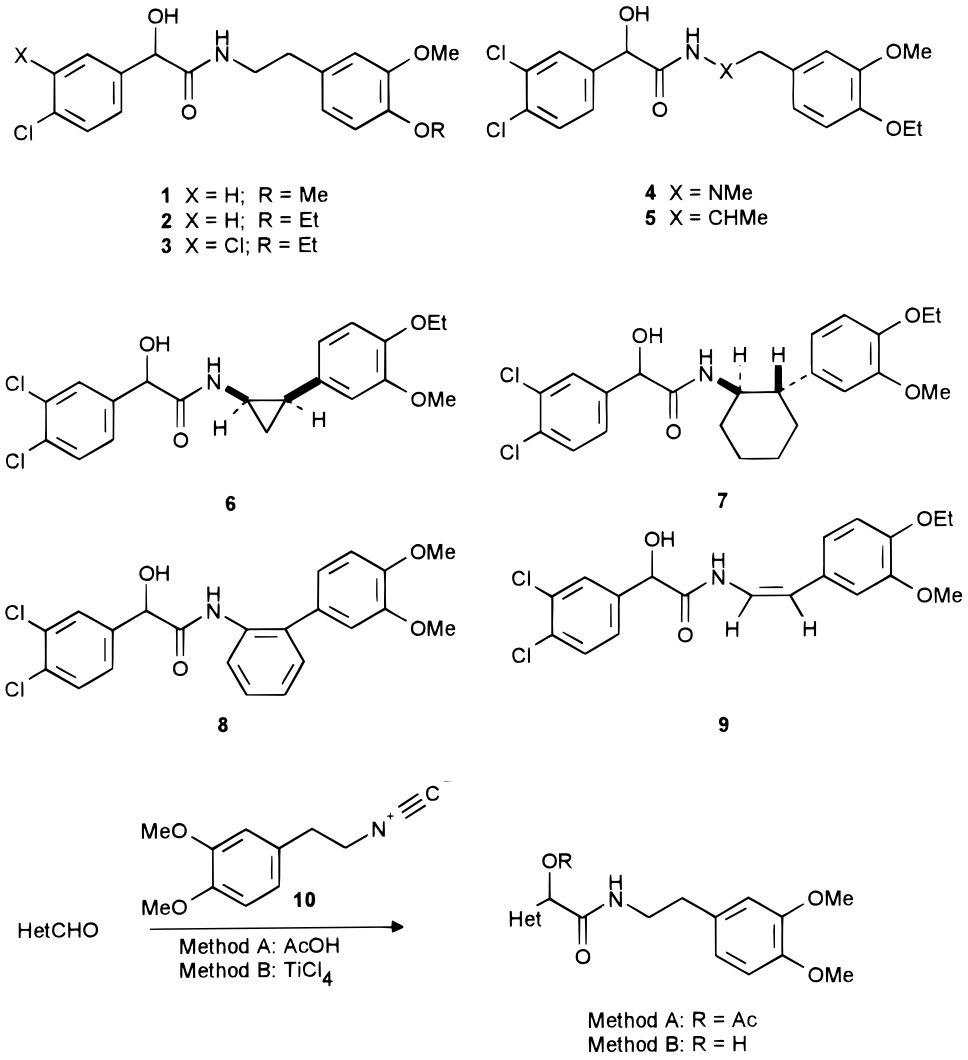

Fig. 1. Structure and synthesis of α-hydroxyarylacetamides.

rotation. When such a non-rigid molecule binds at an enzyme or receptor there is an entropy penalty which must be paid in terms of lowered binding affinity due to loss of free rotation. Consequently, reducing the number of free rotations, for example by introducing a double bond into a chain, can lead to an increased binding affinity at the molecular site of action.[5] The preferred conformations of our compounds were studied using

TABLE 1
Fungicidal Activity of Compound **5** and its stereoisomers

	% *Protectant control* (*mg litre*$^{-1}$)			
	Phytophthora infestans		*Plasmopara viticola*	
	2·5	*1·25*	*2·5*	*1·25*
Diastereomeric mixture[a]	92	83	100	100
(*R*)-α-Methyl-enantiomer A	100	83	100	99
(*S*)-α-Methyl-enantiomer ent-A	0	0	79	54
(*R*)-α-Methyl-enantiomer B	42	50	64	64
(*S*)-α-Methyl-enantiomer ent-B	21	0	69	75
Dimethomorph	100	90	100	95

[a] 1 : 1 mixture of racemates (A + ent-A) and (B + ent-B).

computational (MOPAC AM1 with Chem X) and NMR (Rate of nOe buildup, DMSO as solvent) techniques. The nOe studies, which were performed on compound **2**, proved particularly informative and provided enough information to enable construction of a 3-D model which accounted for the majority of the observed nOe signals (Fig. 2).

In order to test whether or not the nOe derived structure had any biological relevance in terms of binding at the molecular site of action, we synthesised compounds **6**–**9**. All four structures showed reasonable overlap with the nOe structure but the best overlap was shown by the *cis*-cyclopropylamide **6** which encouragingly also showed the best biological activity. Just as importantly the *trans*-isomer of **6**, which did not overlap with the nOe structure, was essentially inactive. In the case of the cyclohexylamide **7** it was the *trans*-isomer which was most active and showed the best overlap. The anilide **8** showed moderate fungicidal activity but surprisingly the related *cis*-eneamide **9**, which overlapped relatively well with the nOe structure, was inactive. Overall, the good biological activity found for the *cis*-cyclopropylamide derivative **6** (comparable to the open-chain compounds) suggests that the nOe derived solution structure is close to that bound at the molecular site of action.

Early structure optimisation work indicated that α-hydroxyheteroarylacetamides were biologically interesting compounds. However, depending on the heterocycle, our existing synthesis routes[2] often failed or were low-yielding. Consequently, a new and more general route was required and the Passerini reaction, involving the reaction of an aldehyde with an isonitrile and a carboxylic acid to give an α-acetoxyacetamide in a single step was investigated. The reaction is well known for benzaldehydes but there is only limited precedent in the literature for its use with heteroaromatic aldehydes.[6–8] The isonitrile **10**[9] was found to react under classical Passerini conditions in the presence of acetic acid with various pyridine, quinoline, pyrimidine, pyrazine and quinoxaline aldehydes to give the required α-acetoxyheteroarylacetamides in 20–50% yield (Fig. 1). Alternatively, the isonitrile **10** could be formed and used *in situ* by dehydration of the *N*-formylphenethylamine with triphosgene.[10] In this case the reaction did not proceed using acetic acid, but worked well in the presence of $TiCl_4$[11] with variously substituted thiophene, thiazole, pyrazole, pyrimidine and 1,2,3-triazole aldehydes to give directly α-hydroxyheteroarylacetamides in 40–80% yield (Fig. 1).[3] Although, in general, this variant gave higher product yields than obtained under classical Passerini conditions, it failed with pyridine aldehydes.

In conclusion, α-hydroxyarylacetamides represent a new class of fungicide with excellent activity against vine downy mildew and late blight. The compounds exhibit good activity against metalaxyl-resistant strains and show long-lasting protectant, curative and translaminar activity. There are indications that they may have a novel mode of action.

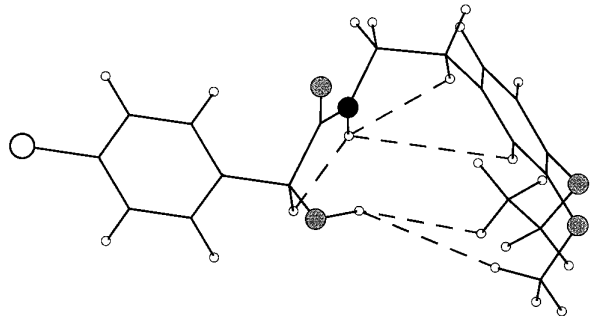

Fig. 2. nOe Derived structure of compound **2**. Important through-space interactions are shown as dashed lines.

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Synthesis and Insecticidal Activity of Heterocyclic Substituted Dihydropyrazoles

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At the beginning of the 1970s, the 3-phenylpyrazoline-1-carboxanilides, such as PH 60-41, were discovered as a new, highly active class of insecticide.[1] In contrast to the benzoylureas such as diflubenzuron, these compounds are not inhibitors of chitin biosynthesis. These new, highly active compounds act on the nervous system by a novel but as yet unknown mechanism.[2,3] During the course of further work in this class an additional phenyl ring was introduced into the 5-position of the pyrazoline, and this led to a further increase in activity.[4] Moving this phenyl ring from the 5- to the 4-position gave PH 60-42[5] with very good insecticidal activity against a broad spectrum of pests, and subsequent work focused mainly on the 3,4-diphenylpyrazolines.[6,7]

The extremely high potential activity coupled with a novel mechanism of action also encouraged us to initiate synthetic work in this class. A thorough review of the literature led us to believe that the 4-position offered the greatest potential for variation. Alkyl, aminoethyl and cyanoethyl groups had all been shown to be tolerated in the position.[8–10] In 1987, pyrazolines were reported with a 4,4-disubstitution in which the phenyl ring was no longer present.[11] RH 3421, in which the 4-position bears a methyl and a carbomethoxy group, was presented as the best derivative.[12] Relatively little was known about heterocyclic substituted pyrazolines. In 1973, pyrazolines substituted in the 5-position by thiophene, pyridine, furan and pyrrole were reported[13] and in 1976 pyrazolines substituted in the 3-position by thiophene.[8] This patent application also claimed pyrazolines substituted in the 4-position by pyridine and thiophene but did not provide any examples.

As heterocycles had hardly been described in the 4-position and up to that point no substitution had been reported in which the substituent was bonded via a hetero-atom to the C-4 atom of the pyrazoline, we decided to start with the synthesis of azole derivatives of pyrazoline bonded via nitrogen to this position. The synthesis of these pyrazolines was carried out by analogy with that of the compounds already reported.[8,13] The azole-substituted acetophenones required, such as the triazole shown in Fig. 1, are easily made from ω-bromoacetophenones and the corresponding azole. Mannich condensation with aqueous formaldehyde (**A**, Fig. 1) provided the unsaturated ketone, which reacted smoothly with hydrazine to give the pyrazoline. Reaction with 4-trifluoromethoxyphenylisocyanate gave **1**, which showed very good activity in our tests at 1 mg litre^{-1} against Plutella and Spodoptera spp. We were able to make a series of azole-substituted pyrazolines by this reaction sequence. An alternative synthesis by reacting the azolyl-acetophenone with *N*,*N*-dimethylmethyleneammonium chloride (**B**, Fig. 1) gave the Mannich base, which was immediately reacted with hydrazine hydrate to yield the pyrazoline.

The corresponding pyrazolines substituted with 6-ring nitrogen heterocycles connected via the nitrogen, such as pyridin-2-one **2** (Fig. 2), were easily made by the analogous route to the azole derivatives, through reaction of 2-hydroxypyridine with bromoacetophenone, for example. The heterocyclic-substituted pyrazolines connected via carbon were made by alternative routes. Thus metallation of 2-methylpyrazine in THF with *n*-butyl-lithium and reaction with methyl 4-chlorobenzoate gave the pyrazine-substituted acetophenone, which yielded the Mannich adduct with *N*,*N*-dimethylmethyleneammonium chloride. Reaction with hydrazine

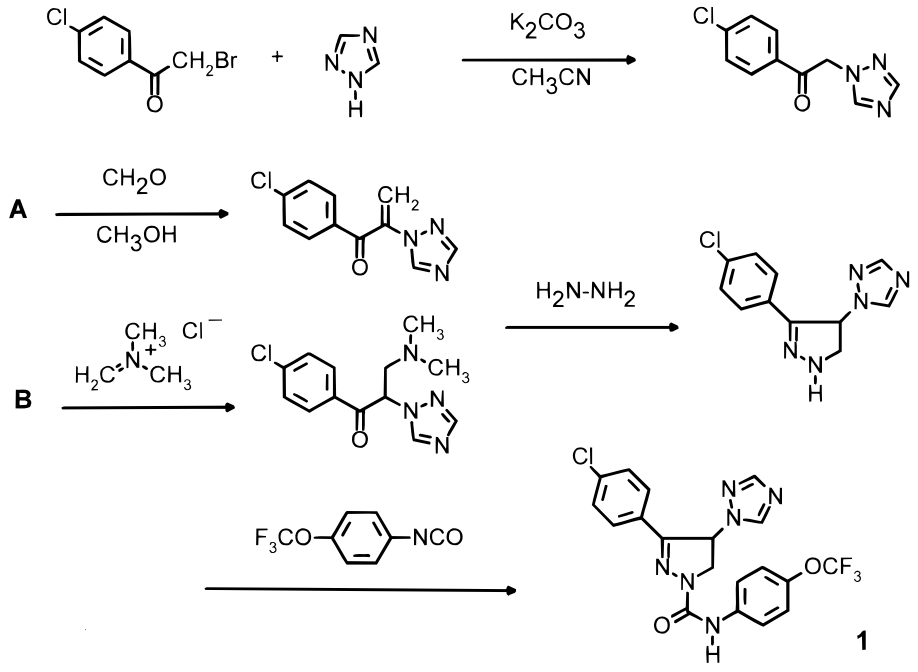
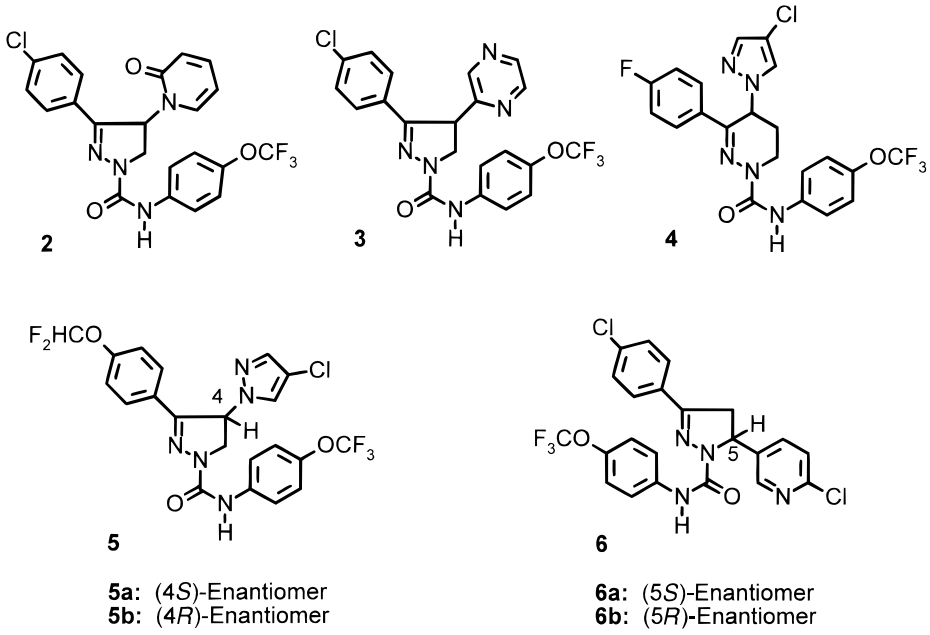


Fig. 1. Synthesis of 4-triazolylpyrazoline-1-carboxanilide.



5a: (4*S*)-Enantiomer
5b: (4*R*)-Enantiomer

6a: (5*S*)-Enantiomer
6b: (5*R*)-Enantiomer

Fig. 2. Structures of compounds referred to in the text.

hydrate gave the pyrazoline substituted in the 4-position by pyrazine in good yield. The carboxanilide **3** (Fig. 2) was obtained by reaction with 4-trifluoromethoxyphenylisocyanate and shows excellent insecticidal activity.

Tetrahydropyridazine-carboxanilides are formally regarded as derivatives of pyrazolines in which the 5-membered ring has been expanded by an additional methylene group. The following route was used for the synthesis. The required 4-chlorobutyrophenones were obtained in good yield by Friedel-Crafts reaction with 4-chlorobutyroyl chloride. These could be brominated easily in the 2-position and then reacted with 4-chloropyrazole in the presence of potassium carbonate, to give the desired 2-pyrazolyl-4-chlorobutyrophenones. These reacted with excess hydrazine hydrate to give the hydrazones, which ring-closed during the reaction with arylisocyanates to form the final products, for example, **4** (Fig. 2). Expanding the pyrazoline ring by inserting a methylene group led to a fall in insecticidal activity.

The heterocyclic pyrazolines were highly effective against beetle larvae and caterpillars. In most species (e.g. *Phaedon cochleariae* F., *Plutella xylostella*, L., Spodoptera and Heliothis spp.) full insecticidal activity in laboratory dip tests was found as low as 8 or 1.6 mg litre^{-1}. The onset of action was somewhat slower than that of pyrethroids or organophosphates but faster than that of IGRs. They have not been found to be cross-resistant to any established class of insecticide on the market.

The structure–activity relationships of 5- and 6-ring heterocycles are outlined in Fig. 3. The best activity resided with the azoles substituted by halogen, bromo- and chloropyrazole being best of all. The 5-chloro-2-pyridyl residue was on the same level as chloropyrazole. 1,2,4-Triazole and pyrazine also had very good activity. The *N*-substituted 2-pyridone was surprisingly good, but pyrimidones were much less active, as was iodopyrazole. Unsubstituted pyrazole, imidazole and pyrimidine were markedly less active, and alkyl substitution was unfavourable.

The structure–activity relationships for the aryl substituents were elucidated. The phenyl ring in the 3-position on the central pyrazoline ring could tolerate a large number of different substituents, although the 4-position was favoured. 3- and 3,4-substitution also led to active compounds. Even with unsubstituted phenyl it was possible to get reasonably active compounds. The best substituents were found to be 4-$OCHF_2$, Br and Cl. In contrast to the phenyl in the 3-position, the phenyl ring of the carboxanilide group was much more sensitive to variation of substitution. Electron-donating substituents such as alkyl or alkoxy groups drastically reduced activity. The unsubstituted phenyl ring was almost inactive. The best activity was shown by 4- and 3,4-substitution; 2-substitution led to loss of activity. The best substituents were electron-withdrawing—4-OCF_3, CF_3, Br or Cl. An additional F or Cl in the 3-position could be tolerated. However, ringing the changes on all three variables might lead to new constellations of substituent combinations with good insecticidal activity.

Apart from the substitution in the 4-position of the pyrazolines, we were also interested in heterocyclic substitution in the 5-position. Pyrazolines substituted in this position by 2-pyridyl, 3-pyridyl and 4-pyridyl had already been described.[13] Reaction of 4-chloroacetophenone with 2-chloro-5-pyridinealdehyde in the presence of potassium hydroxide as base afforded the unsaturated ketone, which reacted smoothly to give the

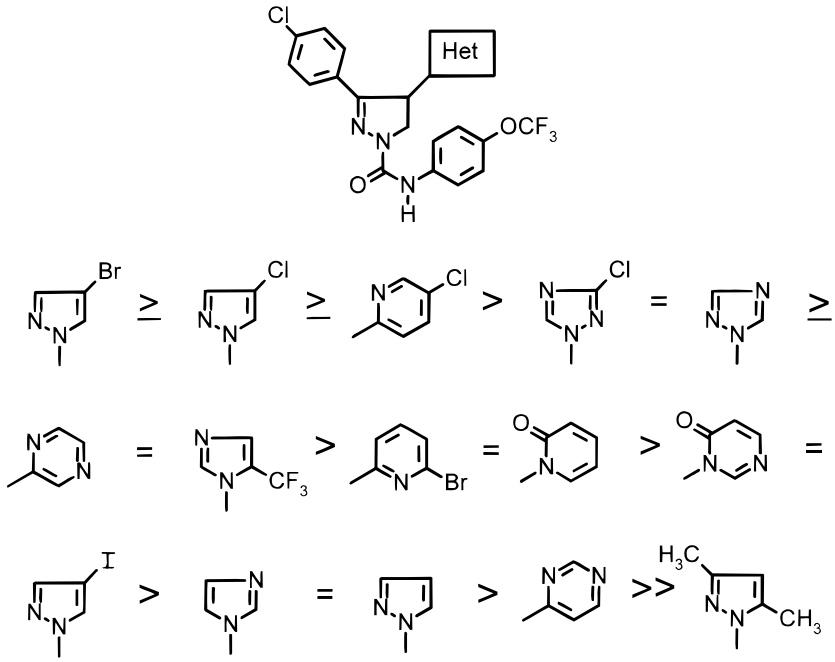


Fig. 3. Structure–activity relationship for heterocycles.

pyrazoline with hydrazine hydrate. The carboxanilide **6** (Fig. 2) showed very good activity against caterpillars.

It had been reported that among the 3,4-aryl-substituted pyrazolines only the (4*S*)-enantiomer is responsible for the insecticidal activity.[14] The enantiomers had been separated via derivatisation to diastereomers. It was therefore particularly interesting to find out whether activity in the series of pyrazolines substituted by azoles in the 4-position is due to a single isomer. As a direct separation of the enantiomers of pyrazolines substituted in the 5-position had not been reported, and as it was also of interest for structure–activity relationships, we separated **6** into its enantiomers. The chromatographic separation of the racemic products **5** and **6** could be achieved with extremely high enantioselectivity on chiral stationary polyamide phases.[15]

X-ray crystal structure analysis was carried out on the separated enantiomers **5a**, **5b** and **6a**, **6b**, and their biological activities studied. The (4*S*)-chloropyrazole enantiomer **5a** contained all the activity, and showed excellent effect in our tests against Spodoptera spp. and Heliothis spp. at 0·32 mg litre^{-1}. The (4*R*)-chloropyrazole enantiomer **5b** was practically inactive. In the case of the pyrazoline substituted in the 5-position by chloropyridine (**6**, Fig. 2), the (5*S*)-enantiomer **6a** was also the sole bearer of the insecticidal activity. When the active (4*S*)-chloropyrazole enantiomer **5a** and the active (5*S*)-chloropyridine enantiomer **6a** were overlaid, it was found that the substituents in the 4- and the 5-positions occupied almost the same space. If the inactive (5*R*)-chloropyridine enantiomer **6b** was laid on top of the active (4*S*)-chloropyrazole enantiomer **5a**, it was found that, in the inactive enantiomer **6b**, the pyridine residue projected into a space on the opposite side of the plane occupied by the (4*S*)-chloropyrazole, and this presumably explains its inactivity.

To summarise, X-ray structural analysis has shown that the same space-filling characteristics are required for insecticidal activity in the 4-substituted and the 5-substituted pyrazolines.

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